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| EXAMINER | |
|---|---|
| HUYNH, PHUONG N | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 07/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/776,232 | KUNDIG ET AL. | |
| | Examiner | Art Unit | |
| | Phuong Huynh | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *38-51, and 60-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-43,45-51 and 60-73* is/are rejected.

7)☒ Claim(s) *44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 38-51, and 60-73 are pending.

2. The following new ground of rejections is necessitated by new reference as stated in the interview on Monday June 7, 2004. The rejections were not made in the Final Office Action mailed May 18, 2004 because the English translation of the Japanese article was not available to the Examiner at the time.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 38-40, 45-47, 49-51, 62-64, and 68-69 are rejected under 35 U.S.C. 102(b) as being anticipated by Sadao *et al* (Biotherapy, 9(7): 845-851, 1995 with English translation; PTO 892).

Sadao *et al* teach a method of inducing CTL response in a mammal such as human and experimental animal tumors having cancer by administering a composition comprising an antigen such as OK-432 obtained as a component of a microorganism (acellular) or tumor antigen such as MAGE-I (polypeptide) in lung cancer and melanomas (page 4) by injecting directly into the lymph nodes (See page 13, BRM immunological action, abstract, page 3, in particular). The reference composition comprising the reference antigen inherently contains a liquid such as buffer since it is impossible to inject solid antigen into the lymph node. The reference antigen is delivered by indwelling reservoir (continuous) or intermittent replacement (repeated) administration directly into the lymph node (See page 11, line 7 from the bottom, in particular). The reference method inherently induces cytotoxic T lymphocyte independent of immunopotentiator. The reference method further comprises delivering a cytokine such as IL2, IFN gamma, and/or TNF (See page 13, last paragraph, page 6, last paragraph, in particular). The reference method of detecting the sustained CTL response in the mammal by measuring the reduction in tumor metastasis (see page 13, line 7 from the bottom, in particular) or CTL assay (page 8, in particular). Thus, the reference teachings anticipate the claimed invention.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 38, 43, 45-46, 48, 65-66, and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sadao *et al* (Biotherapy, 9(7): 845-851, 1995 with English translation; PTO 892) in view of US Pat No. 6,204,250 B1 (of record, March 2001, PTO 892), Coupey *et al* (Cytokine 5(6): 564-9, Nov 1993; PTO 892) and Zinkernagel *et al* (Immunol Rev 156: 199-209, April 1997; PTO 892).

The teachings of Sadao *et al* have been discussed supra.

The claimed invention as recited in claims 43 and 48 differs from the teachings of the reference only in that the method wherein the antigen is provided in the form of a nucleic encoding the antigen.

The claimed invention as recited in claims 65 and 70 differs from the teaching of the reference only in that the method wherein the antigen is provided in the form of a nucleic acid wherein the nucleic acid encoding the antigen comprises a plasmid, a vector or a recombinant viral vector.

The '250 patent, of record, teaches a method of immunizing a mammal such as infant against any target antigen wherein the antigen is delivered in the form of nucleic acid or vector in the host cell that encodes said antigen such as virus or bacteria (See Abstract, column 4, column 7, lines 49-53, claim 14 of '250 patent, in particular). The reference antigen is injected into the infant mammals by any means and route known in the art (See column 8, lines 31-37, in

particular). The reference method of inducing cytotoxic T lymphocytes is obtainable independent of immunopotentiatior since the reference method injected only the reference antigen such as plasmid encoding NPV1 in physiological saline in the absence of immunopotentiator such as adjuvant (See column 9, lines 51, in particular).

Coupey *et al*, of record, teach injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular).

Zinkernagel *et al*, of record, teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antigen as taught by Sadao *et al* for the antigen encoding by nucleic acid or viral or bacterial vector as taught by the '250 patent for a method of inducing CTL response in a mammal as taught by Sadao *et al,* Coupey *et al* and Zinkernagel *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '250 patent teaches that the reference method of inducing cytotoxic T lymphocytes is obtainable independent of immunopotentiatior since the reference method injected only the reference antigen such as plasmid encoding NPV1 in physiological saline the absence of immunopotentiator such as adjuvant (See column 9, lines 51, in particular). Coupey *et al* teach that direct injection of antigen to the popliteal lymph node (axillary lymph node) enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular).

8. Claims 38, 45 and 60-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sadao *et al* (Biotherapy, 9(7): 845-851, 1995 with English translation; PTO 892) in view of US Pat No 5,830,452 A (of record, Nov 1998; PTO 892) and US Pat No 5,279,608 (of record, Jan 1994; PTO 892).

The teachings of Sadao *et al* have been discussed supra.

The claimed invention as recited in claims 60 and 61 differs from the teaching of the reference only in that the method wherein the antigen is maintained by sustained, delivery of the antigen using an external device.

The '452 patent teach a method of obtaining a sustained CTL response such as enhance anti-tumor efficacy by administering cytokine such as IL-2. The '452 patent teach sustained delivery of any compound of interest using a device external to the mammal such as a computer driven pump (See column 5, lines 57-65, in particular). The reference external device is useful for enhancing the therapeutic index of any compound that is useful to stimulate CTL response such as treating tumors, improving patient compliance and minimizing toxicity (See abstract, in particular).

The '608 patent teaches osmotic pump is suitable for the delivery of any agent such as natural synthetic recombinant peptide, protein, drugs analgesics or combination of agents (See column 6, line 32-35, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made continuously repeated deliver any antigen or drug of interest using a computer driven pump as taught by the '452 patent or osmotic pump as taught by the '608 patent for a method of inducing a sustained CTL response wherein the antigen is maintained by sustained, delivery of the antigen as taught by Sadao *et al,* the '452 patent and the '608 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because he '452 patent teaches the therapeutic index is enhanced due to patient compliance and minimize toxicity (See column 5, lines 57-65, in particular). The '608 patent teaches osmotic pump is suitable for the delivery of any agent such as natural synthetic recombinant peptide, protein, drugs analgesics or combination of agents (See column 6, line 32-35, in particular).

9. Claims 38, 45, 65-67 and 70-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sadao *et al* (Biotherapy, 9(7): 845-851, 1995 with English translation; PTO 892) in view of US Pat No 5,853,719 (filed April 30, 1996; PTO 892).

The teachings of Sadao *et al* have been discussed supra.

The claimed invention as recited in claims 66 and 71 differs from the teaching of the reference only in that the vector is a professional antigen-presenting cell.

The claimed invention as recited in claims 67 and 72 differs from the teaching of the reference only in that the vector is a dendritic cell.

The '719 patent teaches a method of administering a vector such as professional antigen cell such as dendritic cell or macrophage that has been loaded with RNA derived from tumors or pathogens as a method of treating cancers and pathogen infections (See entire document, abstract, in particular). The reference antigen presenting cells are useful for inducing CTL response in vivo (col. 12, 65-67, in particular) or in vitro (See col. 12, lines 55-56, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the tumor antigen as taught by Sadao et al for the vector comprising an antigen presenting cells such as such as dendritic cell or macrophage that has been loaded with RNA derived from tumors or pathogens as a method of treating cancers and pathogen infections and directly injecting said vector directly into a lymph node to induce CTL response as taught by Sadao et al for a method of treating cancers as taught by Sadao et al and the '719 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this the '719 patent teaches vector such as professional antigen cell such as dendritic cell or macrophage that has been loaded with RNA derived from tumors or pathogens is useful as a method of treating cancers and pathogen infections (See entire document, abstract, in particular). Sadao *et al* teach direct injection of antigen into a lymph node is useful for inducing CTL response as a method of reducing in tumor metastasis (see page 13, line 7 from the bottom, in particular).

10. Claims 38, 41, 42, 45 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sadao *et al* (Biotherapy, 9(7): 845-851, 1995 with English translation; PTO 892) in view of US Pat No 5,766,601 (Filed April 7, 1995; PTO 892).

The teachings of Sadao *et al* have been discussed supra.

The claimed invention as recited in claim 41 differs from the teaching of the reference only in that the antigen is delivered in a single bolus.

The claimed invention as recited in claims 42 and 73 differs from the teaching of the reference only in that the antigen comprises a microorganism.

The '601 patent teaches a method of stimulating CTL response by administering recombinant microorganism such as influenza virus that expressed the NS-1 antigen to stimulate antigen specific cytotoxic T cell response in vivo (See claims 1-7 of '601, in particular). The '601 patent teaches any recombinant virus is useful for practicing the reference method (See col. 5, lines 46-47, in particular). The '601 patent further teaches that stimulation of cytotoxic T cells is desirable in that these cells will kill cells infected by influenza A virus (See col. 4, lines 66-67, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inject any antigen of interest such as recombinant microorganism such as influenza virus that expressed the NS-1 antigen to stimulate antigen specific cytotoxic T cell response in vivo as taught by the '601 patent by directly injecting said microorganism into a lymph node for a method of inducing CTL response as taught by Sadao et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '601 patent teaches administering recombinant microorganism such as influenza virus that expressed the NS-1 antigen to stimulate antigen specific cytotoxic T cell response in vivo (See claims 1-7 of '601, in particular) and stimulation of cytotoxic T cells is desirable in that these cells will kill cells infected by influenza A virus (See col. 4, lines 66-67, in particular). The recitation of the antigen is administering in a single bolus an obvious variation of the reference teachings and apparent to any one of those ordinary skill in the pharmaceutical art. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454,456,105 USPQ233; 235 (CCPA 1955). See MPEP § 2144.05 part IIA. Therefore, the claimed invention is an obvious variation of the reference teachings, absent a showing of unobvious differences.

11. Claim 44 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

14. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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